Intravenous Hexamethonium Sensitivity and Responses to Oral Treatment

By D. M. Green, M.D., and Eugene J. Ellis, M.D.

This study represents an effort to distinguish between neurogenic and humoral vasoconstrictive factors in a representative group of hypertensive patients by the response to hexamethonium ganglionic blockade. The correlation between intravenous hexamethonium sensitivity and subsequent treatment response was also determined.

One of the most difficult problems in essential hypertension is to select the treatment most apt to benefit the individual patient. Many present-day therapies are believed to act by blocking or depressing some part of the nervous system in the patient with excessive neurogenic vasoconstriction. The effects of cold, sleep and barbiturate administration and spinal anesthesia have been used to select this type of patient for treatment. None of these measures has been conspicuously successful, perhaps because their action is not confined to the neurogenic pressor mechanism or, conversely, is incomplete.

The effect of hexamethonium chloride appears to be limited to a temporary blockade of sympathetic and parasympathetic ganglia. The drug can be given intravenously at any desired concentration and rate. For these reasons, we have used an intravenous hexamethonium test to determine whether patients with excessive neurogenic vasoconstriction could be singled out by their response to autonomic blockade; and, as a corollary, whether the existence of significant non-neurogenic vasoconstriction could be demonstrated by the failure of the blood pressure to fall materially after maximum tolerated doses of hexamethonium. We have also attempted to determine whether the results of oral hexamethonium treatment could be anticipated from the intravenous response.

Methods and Materials

The subjects were 23 patients with essential hypertension, ranging in age from 26 to 72 years. None showed evidences of coronary insufficiency or congestive failure at the time of study. The known duration of the disease ranged from 6 months to 30 years. The status of each patient was evaluated by a complete history and physical examination, x-ray study for heart size, electrocardiogram, urinary concentration test and blood nonprotein nitrogen determination. Funduscopic findings, heart size, and electrocardiographic patterns were graded from 1 to 4. The results of these evaluations indicated that the subject group represented a wide range of hypertensive disease (table 1).

The intravenous hexamethonium test was performed as follows: The height and weight were measured and the surface area calculated. The blood pressure was then determined with a mercury sphygmomanometer at one- to two-minute intervals with the patient sitting. After the pressure had stabilized, a 2 per cent solution of hexamethonium chloride was injected into an antecubital vein. The drug was administered in increments of 1 to 10 mg. every one to three minutes, depending on the patient’s response. Injection of the drug was stopped after the systolic pressure had fallen half-way or more to normal (150 mm. Hg). Following the test, the patient was placed supine until the blood pressure had returned to hypertensive levels. The amount of drug needed to produce the standard fall in pressure was used as the index of sensitivity toward intravenous hexamethonium.

Twenty-one of these subjects were treated with oral hexamethonium chloride for periods of three months.

From the University of Southern California School of Medicine, and Los Angeles County General Hospital, Los Angeles, Calif.

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* We are indebted to Dr. Fredrick F. Younkin of Ciba Pharmaceutical Products, Inc., Summit, New Jersey, for the special preparation of the hexamethonium chloride solution.

† This end-point was chosen because the blood pressure continues to drop for a variable period after intravenous administration is discontinued. As a consequence, irreversible shock from overdosage is a potential hazard.
Table 1.—The Responses of 83 Patients with Essential Hypertension to Intravenous and Oral Hexamethonium in Relation to Their Clinical Status

<table>
<thead>
<tr>
<th>Subject, Initials</th>
<th>Sex</th>
<th>Age (Yrs.)</th>
<th>Surface Area (m²)</th>
<th>Duration (Yrs.)</th>
<th>Final*</th>
<th>Heart Size*</th>
<th>R.G.*</th>
<th>Maxi-</th>
<th>L.V. HXN</th>
<th>Minimum Treatment BP (mm. Hg)</th>
<th>Time of Minimum BP (Days of treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dose (mg./m²)</td>
<td>Pretest BP (mm. Hg)</td>
<td>Posttest BP (mm. Hg)</td>
</tr>
<tr>
<td>A. Y.</td>
<td>x</td>
<td>72</td>
<td>1.39</td>
<td>6.0</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>58</td>
<td>1.4</td>
<td>260 115</td>
<td>2.26</td>
</tr>
<tr>
<td>F. M.</td>
<td>x</td>
<td>38</td>
<td>1.85</td>
<td>3.0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>90</td>
<td>1.6</td>
<td>231 151</td>
<td>1.53</td>
</tr>
<tr>
<td>M. P.</td>
<td>x</td>
<td>41</td>
<td>1.80</td>
<td>1.0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>102</td>
<td>1.7</td>
<td>203 122</td>
<td>1.66</td>
</tr>
<tr>
<td>A. L.</td>
<td>x</td>
<td>43</td>
<td>2.01</td>
<td>12.0</td>
<td>1.5</td>
<td>1</td>
<td>1</td>
<td>104</td>
<td>2.0</td>
<td>201 136</td>
<td>1.48</td>
</tr>
<tr>
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<td>65</td>
<td>1.49</td>
<td>1.0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>107</td>
<td>2.1</td>
<td>175 115</td>
<td>1.55</td>
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<tr>
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<td>53</td>
<td>2.13</td>
<td>0.5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>105</td>
<td>2.3</td>
<td>183 110</td>
<td>1.66</td>
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<tr>
<td>E. H.</td>
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<td>1.64</td>
<td>19.0</td>
<td>2.5</td>
<td>1</td>
<td>2</td>
<td>108</td>
<td>2.4</td>
<td>198 122</td>
<td>1.68</td>
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<tr>
<td>R. D.</td>
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<td>48</td>
<td>1.69</td>
<td>5.0</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>115</td>
<td>2.4</td>
<td>207 123</td>
<td>1.68</td>
</tr>
<tr>
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<td>51</td>
<td>2.02</td>
<td>15.0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>119</td>
<td>2.5</td>
<td>217 133</td>
<td>1.63</td>
</tr>
<tr>
<td>L. S.</td>
<td>x</td>
<td>68</td>
<td>1.28</td>
<td>18.0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>121</td>
<td>3.1</td>
<td>227 102</td>
<td>2.22</td>
</tr>
<tr>
<td>J. J.</td>
<td>x</td>
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<td>1.94</td>
<td>8.0</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>106</td>
<td>3.1</td>
<td>178 136</td>
<td>1.31</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>105</td>
<td>2.2</td>
<td>207 124</td>
<td>1.69</td>
</tr>
</tbody>
</table>

Sensitive Group

| Resistant Group   |     |            |                   |                 |        |             |       | 105    | 2.2      | 207 124           | 1.69                           | 131 92           | 1.48                           | 81 86                      | 2.2 | 145 95 | 120 1.56 | 31 |

Average both groups

- Graded 1 to 4. † During pre-eclamptic episode. Values not included in averages. ‡ Six weeks after cesarean section.
weeks to six months, depending on the severity of side effects and the maintenance of a satisfactory reduction in pressure. The initial dose of 125 or 250 mg., four times daily, was increased by 125 mg. increments to a maximum (when tolerated) of 3 Gm. per day. Throughout treatment the blood pressure was measured at the same time each week in the sitting and standing positions. The lowest blood pressure reached during treatment was used as the measure of the oral therapeutic response. Usually the pressure reverted upward again, despite the continuance of the same or larger oral doses. This secondary rise was interpreted as being the result of the development of tolerance toward the hypotensive effect of hexamethonium; the rapidity with which tolerance developed was gauged by the number of treatment days required to achieve the point of minimum pressure.

**Results**

The pretest blood pressure of the group averaged 208/123. Following intravenous hexamethonium administration, the group pressure fell to 139/98 (fig. 1). The ratio of systolic to diastolic pressure dropped from 1.70, pretest, to 1.45. To determine if this latter change was a specific drug effect, an additional study was made of the ratios found in 75 subjects, both normotensive and hypertensive, under basal conditions (fig. 2). The results demonstrated that the systolic-diastolic ratio was correlated with the level of systolic pressure ($r_{xy} = 0.409$; $t = 3.54; p < 0.0001$). The ratios observed after intravenous hexamethonium administration showed a similar correlation ($r_{xy} = 0.401$; $t = 2.01; p = 0.06$) and appeared to follow the pattern exhibited by individuals with normally low blood pressures.

The mean pulse rate after hexamethonium administration rose from 79 beats per minute, pretest, to 89 at the nadir of the pressure fall. In only four instances did the rate rise above 100.

Individual pressures were reduced to the desired end-point in all subjects, but the hexamethonium requirement varied from 1.4 to 23.0 mg. per square meter of body surface area. Unlike many hypotensive agents, successive increments of hexamethonium did not usually produce a proportional decline in blood pressure. Instead, little or no change in pressure (or pulse rate) ordinarily occurred until a critical level of dosage was approached. Its imminence was usually heralded by a transitory dip in pressure and by sighing. The subsequent one or two drug increments were followed by an abrupt and marked drop, which continued after the injection had been stopped. In 17 instances the pressure declined into or below the normal range, with a return to hypertensive levels 1 to 45 minutes after the

**Fig. 1.** Blood pressure and pulse rate in a group of 23 hypertensive subjects before and after the intravenous injection of hexamethonium chloride. **SBP** = systolic blood pressure (millimeters Hg); **MBP** = mean blood pressure (average of systolic and diastolic; millimeters Hg); **DBP** = diastolic blood pressure (millimeters Hg); **S/D** = systolic-diastolic pressure ratio; **P** = pulse rate (beats per minute).

**Fig. 2.** Relation of systolic-diastolic pressure ratio to systolic blood pressure in 75 hypertensive and normotensive subjects under basal conditions (solid circles) as compared with 23 hypertensive subjects after intravenous hexamethonium injection (open circles). The broken lines represent the regressions from the X and Y axes in the basal group. ($r_{xy} = 0.409; t = 3.54; p < 0.0001$).
patient had been placed in the supine position. The minimum value to which the blood pressure fell and the time required for recovery were, in general, inversely proportional to the total dose; the larger the dose needed to lower the pressure, the smaller was the tendency toward a postinjection decline into or below the normotensive range, and the more rapid was the reversion to hypertensive levels.

The large variation in the amount of drug required by different subjects led us to look for possible correlations. Accordingly, the subjects were divided into "sensitive" and "resistant" groups, representing the upper and lower halves of the hexamethonium dosage range, respectively (table 1). The dividing line between the two groups lay at approximately 4 mg. of hexamethonium chloride per square meter of body surface area. The quantitative values of the various clinical characteristics were also averaged and the two groups were compared. Where differences in means were found, their significance was evaluated by the $t$ test.

The results of these calculations failed to demonstrate significant differences in pretest blood pressure, pulse rate, heart size, electrocardiographic patterns, funduscopic changes or known duration of hypertension. The only suggestive differences were the slightly greater
which is to say that the smaller the intravenous dose required, the greater was the maximum reduction in pressure under oral treatment. The subject group which was sensitive to intravenous hexamethonium responded to oral therapy by a blood pressure reduction to normal (fig. 3). In contrast, the resistant subjects as a group showed a maximum fall to 177 mm. Hg systolic, 105 mm. diastolic.

The sensitive group also differed from the resistant group in the frequency of postural hypotension during oral therapy, as evidenced by a marked drop in pressure between the sitting and standing positions, and by orthostatic dizziness and syncope. One or both signs occurred in 6 of 10 sensitive subjects, as compared with 2 of 11 resistant individuals. Parasympatholytic side effects were about equally prominent in the two groups, indicating that variations in absorption were not responsible for the lack of hypotensive activity in the resistant group.

A third difference between groups was the rapidity with which tolerance was developed for the hypotensive effect during oral therapy. The maximum reduction in pressure was reached early in the resistant group, after an average treatment period of two and one half weeks. In the sensitive group, on the other hand, the pressure continued to fall for about four and one half weeks, and the subsequent escape to hypertensive levels was slow.

Neither group developed much tolerance for parasympatholytic side effects. The drug usually had to be discontinued because of failure to maintain a pressure reduction commensurate with the difficulties of constipation, xerostomia, blurred vision or urinary retention.

The results in the two groups are typified by the favorable clinical course of a sensitive individual (fig. 4), and the failure of response in a resistant subject (fig. 5), who received the same daily doses of oral hexamethonium chloride.

**Discussion**

The results of this study indicate that hypertensive patients can be classified as sensitive or resistant to the hypotensive action of hexamethonium chloride on the basis of the amount of intravenous drug required to produce a standard fall in pressure. No completely satisfactory explanation for this variation in sensitivity was found in the clinical status of these patients. One of the responsible factors appeared to be an impairment of renal excretory function. Under these circumstances a delay in metabolism and excretion of the drug may have made a smaller dose more effective and persistent as a ganglionic blocking agent.

None of the findings suggested that any major part of the hypertension in these subjects was due to vasoconstriction which was not under autonomic control. The blood pressure of both sensitive and resistant subjects was brought into the normal range with about equal frequency, when sufficient hexamethonium chloride was injected. The minimal rise in pulse rate during hexamethonium-induced hypotension indicated that cardioaccelerator, as well as vasoconstrictor fibers, were blocked effectively in the great majority of both sensitive and resistant subjects. The results do not exclude the possibility that autonomic control of vasoconstriction may be mediated through humoral factors. In support of this possibility is Grimson's finding that experimental neurogenic hypertension persisted in otherwise completely sympathectomized dogs until the autonomic nerve supply to the kidneys was cut; whereupon blood pressure fell to normal limits.

The therapeutic responses in these subjects suggest that the intravenous hexamethonium test may have use as a guide to the maximum pressure reduction which can be anticipated from oral treatment, and to the rapidity with which tolerance may develop for the hypotensive action. The reported failure of others to correlate intravenous sensitivity and oral effectiveness may have been due to differences in the criteria used to quantitate these actions. The rapid development of tolerance for the oral hypotensive effect makes the therapeutic evaluation particularly difficult.

**Summary and Conclusions**

Twenty-three hypertensive subjects were tested with intravenous hexamethonium
chloride in an effort to determine the frequency and extent of blood pressure elevation not susceptible to reduction by ganglionic blockade. Twenty-one of the subjects were also studied to find out if the responses to oral hexamethonium therapy could be anticipated from the amount of intravenous drug required to produce a standard (50 per cent) fall in pressure.

The intravenous dose needed to produce this standard reduction varied from 1.4 to 23.0 mg. per square meter of body surface area. A comparison of the clinical characteristics of the "sensitive" and "resistant" halves of the group (as determined by a dosage requirement of less or more than 4 mg. per square meter, respectively) failed to show differences in pretest systolic or diastolic blood pressure, pulse rate, heart size, electrocardiographic patterns or known duration of the disease. "Sensitive" subjects were, in general, somewhat older and had suffered a greater deterioration in renal excretory function. Delay in renal metabolism or excretion of hexamethonium appeared to be one of the factors which may have been responsible for the differences in individual sensitivity.

No "irreversible" hypertensions were encountered. Nor was any evidence secured that a major part of the hypertension in any subject was due to vasoconstriction not under autonomic control. Reductions to normal were about equally frequent in sensitive and resistant subjects when sufficient hexamethonium was injected.

During oral hexamethonium treatment the "sensitive" group showed a reduction to normal pressure levels, a high incidence of postural hypotensive reactions and a delayed development of tolerance for the hypotensive effect. In contrast, the "resistant" group showed a much smaller maximum fall in pressure, a low incidence of postural hypotension and rapid development of tolerance for the hypotensive effect.

On the basis of these results, it is concluded that the intravenous hexamethonium test may be of some use in anticipating the responses of patients to oral hexamethonium treatment.

**Sumario Español**

Este estudio representa un esfuerzo para distinguir entre los factores vasoconstrictores humorales y neurogénicos en un grupo representativo de pacientes hipertensos mediante la repuesta al bloqueo ganglionar del hexamethonium. La correlación entre la sensibilidad al hexamethonium intravenoso y la repuesta a tratamiento subsiguiente también se determinó.

**REFERENCES**

1. **Miller, J. H., and Brugir, M.:** Cold-pressor reaction in normal subjects and in patients with primary (essential) and secondary (renal) hypertension. Am. Heart J. 18: 329, 1939.
7. **Graeme, J. L.:** Personal communication.
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